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OCT 31 2001

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*LIMITED TO MATTERS
AND PROCEEDINGS BEFORE
FEDERAL COURTS & AGENCIES
**REGISTERED PATENT AGENT
***SENIOR COUNSEL

October 31, 2001

WRITER'S DIRECT NUMBER:

(202) 789-5525

INTERNET ADDRESS:

BRIAND@SKGF.COM

Attn: Art Unit 1631

Commissioner for Patents
Washington, D.C. 20231

Re: U.S. Utility Continuation Application
Appl. No. 09/848,353; Filed: May 4, 2001
For: **Modulating the Permeability of a Physiological Barrier with an
Agent that Modulates Tyrosine Phosphorylation (As Amended)**
Inventors: Staddon *et al.*
Our Ref: 0623.0410001/EKS/BJD

Sir:

Transmitted herewith for appropriate action are the following documents:

1. Information Disclosure Statement (*in duplicate*);
2. 19 pages of Form PTO-1449 citing 60 documents;
3. A copy of each of the 60 cited documents; and
4. One (1) return postcard.

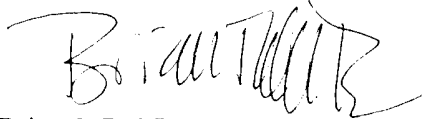
It is respectfully requested that the attached postcard be stamped with the date of filing of these documents, and that it be returned to our courier. In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned.

Commissioner for Patents
October 31, 2001
Page 2

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036. A duplicate copy of this letter is enclosed.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Brian J. Del Buono
Attorney for Applicants
Registration No. 42,473

BJD/nef
Enclosures

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Staddon *et al.*

Appl. No. 09/848,353

Filed: May 4, 2001

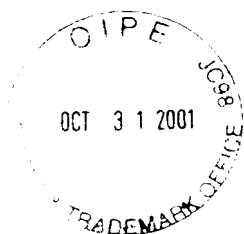
For: **Modulating the Permeability of a
Physiological Barrier with an
Agent that Modulates Tyrosine
Phosphorylation** (As amended)

Confirmation No. 1015

Art Unit: 1631

Examiner: To be assigned

Atty. Docket: 0623.0410001/EKJJD



Information Disclosure Statement

Commissioner for Patents
Washington, D.C. 20231

Sir:

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. A copy of each of these documents is provided.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. However, the Examiner's attention is directed specifically to Document AT7, John, V. *et al.*, *Pharm. Pharmacol. Lett.* 3:190-193 (1994), for which the month of publication could not be determined after diligent efforts by the undersigned. Applicants have listed publication dates on the attached PTO-1449 based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Document AM1, Japan Patent Office Publication No. 4-13631, assigned to Tonen Corporation and Eisai KK, discloses the purification and characterization of a substance from *Anacardium occidentale* that has tyrosine kinase-inhibiting activity and that may be useful in treating or preventing cancer metastasis. A copy of the abstract of this publication in the English language (from Derwent WPI) is included herewith as Reference Number AT19.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith. It is further understood that the Examiner will consider information that had been cited or submitted to the U.S. Patent and Trademark Office in a prior application relied on under 35 U.S.C. § 120. 1138 OG 37, 38 (May 19, 1992).

It is respectfully requested that the Examiner initial and return a copy of the enclosed PTO-1449, and to indicate in the official file wrapper of this patent application that the documents have been considered.

This Information Disclosure Statement is being filed before the mailing date of a first Office Action on the merits. No statement or fee is required.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036. A duplicate copy of this pleading is enclosed.

Respectfully submitted,

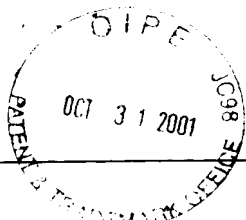
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Brian J. Del Buono
Attorney for Applicants
Registration No. 42,473

Date: Oct. 31, 2001

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INFORMATION DISCLOSURE STATEMENT

FORM PTO-1449

ATTY. DOCKET NO.
0623.0410001/EKS/BJDAPPLICATION NO.
09/848,353APPLICANT
Staddon et al.FILING DATE
May 4, 2001GROUP
1631

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB- CLASS	FILING DATE
	AA1	5,155,031	10/13/92	Posner et al.	435	184	06/07/90
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FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB- CLASS	TRANSLATION
	AL1	WO 91/04745	04/18/91	WIPO			Yes No
	AM1	JP 4-13631	01/17/92	Japan			Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	1	Anderson, J.M., et al., "The structure and regulation of tight junctions," <i>Curr. Opin. Cell Biol.</i> 5(5):772-778, Current Biology Ltd. (October 1993).
	AS	1	Balda, M.S., et al., "Assembly of the Tight Junction: The Role of Diacylglycerol," <i>J. Cell Biol.</i> 123(2):293-302, The Rockefeller University Press (October 1993).
	AT	1	Behrens, J., et al., "Loss of Epithelial Differentiation and Gain of Invasiveness Correlates with Tyrosine Phosphorylation of the E-Cadherin/ β -Catenin Complex in Cells Transformed with a Temperature-sensitive v-SRC Gene," <i>J. Cell Biol.</i> 120(3):757-766, The Rockefeller University Press (February 1993).

EXAMINER

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EXAMINER: Initial if reference considered, whether or not citation is in conformance with RPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

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		AL					Yes No
		AM					Yes No
		AN					Yes No
		AO					Yes No
		AP					Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AF	<u>2</u>	Citi, S., "Protein Kinase Inhibitors Prevent Junction Dissociation Induced by Low Extracellular Calcium in MDCK Epithelial Cells," <i>J. Cell Biol.</i> 117:169-178, The Rockefeller University Press (April 1992).
	AS	<u>2</u>	Citi, S., et al., "The role of phosphorylation in the assembly and disassembly of epithelial junctions," <i>Molec. Biol. Cell</i> 3(Suppl.):218a, Abstract No. 1262, The American Society for Cell Biology (September 1992).
	AT	<u>2</u>	Collares-Buzato, C.B., et al., "Junctional uvomorulin/E-cadherin and phosphotyrosine-modified protein content are correlated with paracellular permeability in Madin-Darby canine kidney (MDCK) epithelia," <i>Histochemistry</i> 101:135-194, Springer-Verlag (1994).

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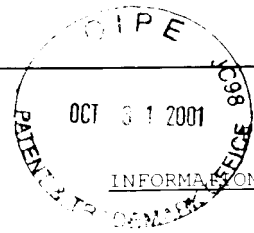
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	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AE	<u>3</u>	Crow, D.S., et al., "Phosphorylation of connexin43 in cells containing mutant <i>src</i> oncogenes," <i>Oncogene</i> 7:993-1003, Nature Publishing Group (May 1992).
	AS	<u>3</u>	Downing, J.R., and Reynolds, A.B., "PDGF, CSF-1, and EGF induce tyrosine phosphorylation of p120, a pp60 ^{src} transformation-associated substrate," <i>Oncogene</i> 6:607-613, Nature Publishing Group (1991).
	AT	<u>3</u>	Durieu-Trautmann, O., et al., "Nitric Oxide and Endothelin Secretion by Brain Microvessel Endothelial Cells: Regulation by Cyclic Nucleotides," <i>J. Cell. Physiol.</i> 155(1):104-111, Wiley-Liss, Inc. (April 1993).

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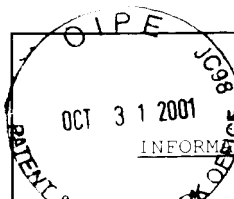
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	AN						Yes No
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	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

AF	<u>4</u>	Fantus, I.G., et al., "Pervanadate [Peroxide(s) of Vanadate] Mimics Insulin Action in Rat Adipocytes via Activation of the Insulin Receptor Tyrosine Kinase," <i>Biochemistry</i> 28:8864-8871, American Chemical Society (1989).
AS	<u>4</u>	Filson, A.J., et al., "Tyrosine Phosphorylation of a Gap Junction Protein Correlates with Inhibition of Cell-to-Cell Communication," <i>Cell Growth Differ.</i> 1:661-668, American Association for Cancer Research (1990).
AT	<u>4</u>	Galaktionov, K., and Beach, D., "Specific Activation of cdc25 Tyrosine Phosphatases by B-Type Cyclins: Evidence for Multiple Roles of Mitotic Cyclins," <i>Cell</i> 67:1181-1194, Cell Press (1991).

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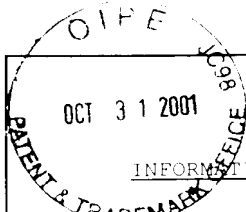
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OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>5</u>	Garcia-Morales, P., et al., "Tyrosine phosphorylation in T cells is regulated by phosphatase activity: Studies with phenylarsine oxide," <i>Proc. Natl. Acad. Sci. USA</i> 87:9255-9259, The National Academy of Sciences (1990).
	AS	<u>5</u>	Gumbiner, B., and Simons, K., "A Functional Assay for Proteins Involved in Establishing an Epithelial Occluding Barrier: Identification of a Uvomorulin-like Polypeptide," <i>J. Cell Biol.</i> 102:457-468, The Rockefeller University Press (1986).
	AT	<u>5</u>	Gumbiner, B., et al., "The Role of the Cell Adhesion Molecule Uvomorulin in the Formation and Maintenance of the Epithelial Junctional Complex," <i>J. Cell Biol.</i> 107:1575-1587, The Rockefeller University Press (1988).

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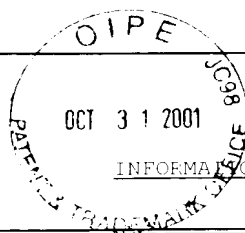
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	AN						Yes No
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	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>6</u>	Hamaguchi, M., et al., "p60 ^{src} causes tyrosine phosphorylation and inactivation of the N-Cadherin-catenin cell adhesion system," <i>EMBO J.</i> 12(1):307-314, Oxford University Press (January 1993).
	AS	<u>6</u>	Hedrick, L., et al., "Cell adhesion molecules as tumour suppressors," <i>Trends Cell Biol.</i> 3(2):36-39, Elsevier Science Ltd. (February 1993).
	AT	<u>6</u>	Heffetz, D., et al., "The Insulinomimetic Agents H ₂ O ₂ and Vanadate Stimulate Protein Tyrosine Phosphorylation in Intact Cells," <i>J. Biol. Chem.</i> 265:2896-2902, The American Society for Biochemistry and Molecular Biology, Inc. (1990).

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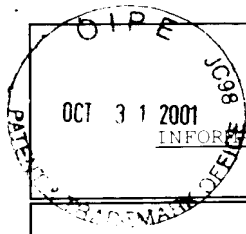
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OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

AR	7	Herrenknecht, K., et al., "Endothelial Cadherins And The Regulation Of Tight Junction Permeability," Abstract (distributed at meeting) from British Society for Immunology Spring Meeting 1994, University of Southampton, United Kingdom, March 23-25, 1994.
AS	7	Izumi, T., et al., "Periodic Changes in Phosphorylation of the <i>Xenopus</i> cdc25 Phosphatase Regulate Its Activity," <i>Mol. Biol. Cell</i> 3:927-939, American Society for Cell Biology (1992).
AT	7	John, V., et al., "The effect of cyclic AMP-dependent protein kinase inhibitors on electrical resistance in the cell culture model for the blood-brain barrier," <i>Pharm. Pharmacol. Lett.</i> 3(5):190-193, Springer-Verlag (1994).

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OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AP	<u>8</u>	Kanner, S.B., et al., "Tyrosine Phosphorylation of a 120-Kilodalton pp60 ^{src} Substrate upon Epidermal Growth Factor and Platelet-Derived Growth Factor Receptor Stimulation and in Polyomavirus Middle-T-Antigen-Transformed Cells," <i>Mol. Cell. Biol.</i> 11:713-720, American Society for Microbiology (1991).
	AS	<u>8</u>	Furihara, H., et al., "Increased Tyrosine Phosphorylation Accompanies Modification of Tight Junctions Between Foot Processes of Glomerular Epithelial Cells (GEC)," <i>Mol. Biol. Cell</i> 3(Suppl.):218a, Abstract No. 1263, American Society for Cell Biology (1992).
	AT	<u>8</u>	Furihara, H., et al., "Localization and Dynamics of Tight Junction Protein, ZO-1 in Rat Glomerular Epithelial Cells," <i>Cell Struct. Funct.</i> 17(6):493, Abstract No. 1D-1615, Japan Society of Cell Biology (1992).

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OIPE OCT 31 2001 RECEIVED MAIL ROOM	FORM PTO-1449		ATTY. DOCKET NO. 0623.0410001/EKS/BJD	APPLICATION NO. 09/848,353
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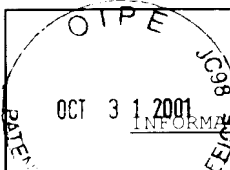
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	AR	<u>9</u>	Langeler, E.G., and van Hinsbergh, V.W.M., "Norepinephrine and iloprost improve barrier function of human endothelial cell monolayers: role of cAMP," <i>Am. J. Physiol.</i> 260:c1052-c1059, American Physiological Society (1991).
	AS	<u>9</u>	Levenson, R.M., and Blackshear, P.J., "Insulin-stimulated Protein Tyrosine Phosphorylation in Intact Cells Evaluated by Giant Two-dimensional Gel Electrophoresis," <i>J. Biol. Chem.</i> 264:19984-19993, The American Society for Biochemistry and Molecular Biology (1989).
	AT	<u>9</u>	Liebow, C., et al., "Somatostatin analogues inhibit growth of pancreatic cancer by stimulating tyrosine phosphatase," <i>Proc. Natl. Acad. Sci. USA</i> 86:2003-2007, The National Academy of Sciences (1989).

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	FORM PTO-1449		ATTY. DOCKET NO. 0623.0410001/EKS/BJD	APPLICATION NO. 09/848,353
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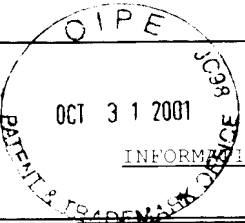
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OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>10</u>	Linder, M.E., and Burr, J.G., "Nonmyristoylated p60 ^{v-src} Fails to Phosphorylate Proteins of 115-120 kDa in chicken embryo fibroblasts," <i>Proc. Natl. Acad. Sci. USA</i> 85:2608-2612, The National Academy of Sciences (1988).
	AS	<u>10</u>	Lum, H., and Malik, A.B., "Mechanisms of increased endothelial permeability," <i>Can. J. Physiol. Pharmacol.</i> 74:787-800, NEC Canada (1996).
	AT	<u>10</u>	Madara, J.L., "Tight Junction Dynamics: Is Paracellular Transport Regulated?," <i>Cell</i> 53:497-498, Cell Press (1998).

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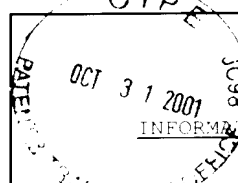
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AF	<u>11</u>	Martinez-Palomo, A., et al., "Experimental Modulation of Occluding Junctions in a Cultured Transporting Epithelium," <i>J. Cell Biol.</i> 87:736-745, The Rockefeller University Press (1980).
AS	<u>11</u>	Matsuyoshi, N., et al., "Cadherin-Mediated Cell-Cell Adhesion Is Perturbed by v-src Tyrosine Phosphorylation in Metastatic Fibroblasts," <i>J. Cell Biol.</i> 118:703-714, The Rockefeller University Press (August 1992).
AT	<u>11</u>	Morgan, L., et al., "Molecular Control of Blood Brain Barrier Permeability," Abstract (distributed at meeting) from 8th International Workshop on in Vitro Toxicology, Zurich, Switzerland, September 20-23, 1994.

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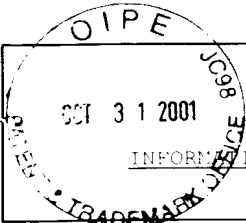
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	AP	<u>12</u>	Mullin, J.M., et al., "Modulation of tumor necrosis factor-induced increase in renal (LLC-PK ₁) transepithelial permeability," <i>Am. J. Physiol.</i> 263:F915-F924, American Physiological Society (November 1992).
	AS	<u>12</u>	Musil, L.S., et al., "Differential Phosphorylation of the Gap Junction Protein Connexin43 in Junctional Communication-competent and -deficient Cell Lines," <i>J. Cell Biol.</i> 111:2077-2088, The Rockefeller University Press (1990)
	AT	<u>12</u>	Ojakian, G.K., "Tumor Promoter-Induced Changes in the Permeability of Epithelial Cell Tight Junctions," <i>Cell</i> 23:95-103, MIT (1981).

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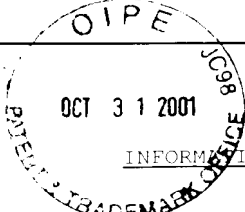
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	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

AP	<u>13</u>	Feralta Soler, A., et al., "Tissue remodeling during tumor necrosis factor-induced apoptosis in LLC-FK, renal epithelial cells," <i>Am. J. Physiol.</i> 270:F869-F879, American Physiological Society (1996).
AS	<u>13</u>	Fubin, L.L., et al., "A Cell Culture Model of the Blood-Brain Barrier," <i>J. Cell Biol.</i> 115:1725-1735, The Rockefeller University Press (1991).
AT	<u>13</u>	Fubin, L.L., et al., "Endothelial cells: adhesion and tight junctions," <i>Curr. Opin. Cell Biol.</i> 4:830-833, Current Biology Ltd. (October 1992).

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	FORM PTO-1449		ATTY. DOCKET NO. 0623.041.001/EKS/BJD	APPLICATION NO. C9/848,353
	INFORMATION DISCLOSURE STATEMENT		APPLICANT Staddon et al.	
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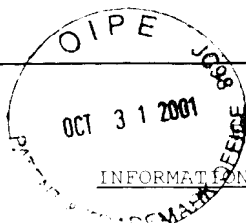
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AF	<u>14</u>	Fubin, L.L., and Staddon, J.M., "Regulation Of Blood-Brain Barrier Permeability," Abstract (distributed at meeting) from XXXII International Union of Physiological Sciences (IUPS) Congress, Glasgow, UK, August 4-6, 1993.
AS	<u>14</u>	Fubin, L.L., et al., "Tight Junctions And The Blood-Brain Barrier," Abstract (distributed at meeting) from Association pour la Recherche sur La Sclerose en Plaques (ARSEP), Paris, France, December 1-2, 1993.
AT	<u>14</u>	Fubin, L.L., et al., "Signal Transduction And The Blood-Brain Barrier," Abstract (distributed at meeting) from 17th Annual Meeting of the European Neuroscience Association, Vienna, Austria, September 4-8, 1994.

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AF	15	Fubin, L.L., et al., "Tight Junctions and the Blood-Brain Barrier," in: Cell Culture in Pharmaceutical Research, Fusenig, N.E., and Graf, H., eds., Berlin: Springer-Verlag, pp. 69-77 (October 1994).
AS	15	Fubin, L.L., et al., "Signal Transduction in Brain Endothelial Cells," Paper (distributed at meeting) presented at INSERM Meeting No. 67, In Vitro Models for Drug Transport Across Epithelial and Endothelial Barriers, Le Vesinet, France, October 13-14, 1994.
AT	15	Futten, M.J., et al., "Electrical resistance and macromolecular permeability of brain endothelial monolayer cultures," <i>Brain Res.</i> 425:301-310, Elsevier Science (1987).

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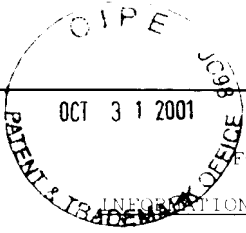
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AF	<u>16</u>	Staddon, J.M., et al., "Tyrosine Phosphatase Inhibitors Increase Tight Junctional Permeability in Strain I MDCK Cells," <i>Mol. Biol. Cell</i> 4(Suppl.):103a, Abstract No. 599, American Society for Cell Biology (October 1993).
AS	<u>16</u>	Staddon, J.M., et al., "Tyrosine Phosphorylation and Tight Junction Permeability. I," Abstract (distributed at meeting) from Autumn Meeting of the British Society for Cell Biology, University of Oxford, UK, September 18-21, 1994.
AT	<u>16</u>	Staddon, J.M., et al., "Evidence that tyrosine phosphorylation may increase tight junction permeability," <i>J. Cell Sci.</i> 108(2):609-619, The Company Of Biologists Ltd. (1995).

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	AR	<u>17</u>	Stelzner, T.J., et al., "Role of Cyclic Adenosine Monophosphate in the Induction of Endothelial Barrier Properties," <i>J. Cell. Physiol.</i> 139:157-166, Alan R. Liss, Inc. (1989).
	AS	<u>17</u>	Stevenson, B.R., et al., "Phosphorylation of the Tight-junction protein ZO-1 in two strains of Madin-Darby canine kidney cells which differ in transepithelial resistance," <i>Biochem. J.</i> 263:597-599, Portland Press Ltd. (1989).
	AT	<u>17</u>	Swenson, K.I., et al., "Tyrosine phosphorylation of the gap junction protein connexin43 is required for the pp60 ^{src} -induced inhibition of communication," <i>Cell Regul.</i> 1:989-1002, The American Society for Cell Biology (1990).

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	AF	<u>18</u>	Tsukita, S., et al., "Specific Proto-Oncogenic Tyrosine Kinases of src Family Are Enriched in Cell-to-Cell Adherens Junctions Where the Level of Tyrosine Phosphorylation Is Elevated," <i>J. Cell Biol.</i> 113:867-879, The Rockefeller University Press (1991).
	AS	<u>18</u>	Tsukita, S., et al., "Submembranous Junctional Plaque Proteins Include Potential Tumor Suppressor Molecules," <i>J. Cell Biol.</i> 123(5):1049-1053, The Rockefeller University Press (December 1993).
	AT	<u>18</u>	Volberg, T., et al., "The effect of tyrosine-specific protein phosphorylation on the assembly of adherens-type junctions," <i>EMBO J.</i> 11:1733-1742, Oxford University Press (May 1992).

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	AP	<u>19</u>	Warren, S.L., and Nelson, W.J., "Nonmitogenic Morphoregulatory Action of pp60 ^{v-src} on Multicellular Epithelial Structures," <i>Mol. Cell. Biol.</i> 7:1326-1337, American Society for Microbiology (1987).
	AS	<u>19</u>	Uehara, Y. et al., "Irreversible Inhibition Of V-SRC Tyrosine Kinase Activity By Herbimycin A And Its Abrogation By Sulfhydryl Compounds," <i>Biochem. Biophys. Res. Commun.</i> 163:803-809, Academic Press, Inc. (1989).
	AT	<u>19</u>	English-language abstract for Japanese patent document No. JP 4-13631 (Doc. Ref. No. AML), Derwent WPI Accession No. 8942154.

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